(12) UK Patent Application (19) GB (11) 2 217 319 (13) A

(43) Date of A publication 25.10.1989

(21) Application No 8809162.4

(22) Date of filing 19.04.1988

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(51) INT CL⁴
C07C 101/02, C07D 471/04 489/02 491/14

(52) UK CL (Edition J)
C2C CAA CKM CLR C1483 C1504 C155X C20Y
C213 C214 C236 C247 C25Y C250 C251 C255
C282 C29X C29Y C30Y C31Y C314 C32Y C321
C339 C34Y C342 C351 C352 C36Y C360 C361
C362 C364 C366 C367 C368 C43X C45X C45Y
C490 C491 C584 C62X C620 C623 C628 C630
C634 C638 C65X C650 C658 C67X C672 C802
C805 C808
U1S S1310 S1343 S1427

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CA 53:242d

(58) Field of search
Chemical Abstracts

(54) **Racemic and optically active fatty amino acids, their homo-and hetero-oligomers and conjugates, the pr cess of their production, their pharmaceutical composition and activity**

(57) Racemic and optically active compounds, their salts and therapeutic compositions of general formula 1

$$X\text{-}[(NH\text{-}CHR_1\text{-}CO)_N\text{-}Z\text{-}(NH\text{-}CHR_2\text{-}CO)_M)]_pY$$

to be used as pharmaceutical formulation components, surface active agents, intrinsic pharmaceutical and immunological agents or cosmetics.

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RACEMIC AND OPTICALLY ACTIVE FATTY AMINO ACIDS, THEIR HOMO- AND HETERO-OLIGOMERS AND CONJUGATES, THE PROCESS OF THEIR PRODUCTION, THEIR PHARMACEUTICAL COMPOSITION AND ACTIVITY

CHEMISTRY

1. Preparation of fatty amino acids

The fatty amino acids (6-24 carbon atoms) were synthesised by literature methods (Albertson, N., F. :J. Am. Chem. Soc. 1946, 68, 450). Owing to the poor solubility of the amino acids with more than twelve carbon atoms, the synthesis of the compounds by the literature methods gave very low yields.

However, when hydrolysis and decarboxylation of the alkyl-diethylacetamido malonates were carried out in the presence of DMF, the yields were increased to 95% and the amino acids obtained in very high purity.

Thus, starting from the corresponding alkyl bromide after the

reaction with diethylacetamido-malonate, followed by HCL/H_2O/DMF hydrolysis and decarboxylation we have synthesised fatty amino acids with 6-24 carbon atoms. This new method is industrially usable and safe. Resolution of the racemic compounds has been achieved enzymatically and by chemical methods.

2. Synthesis of homo-oligomers of fatty amino acids

Standard solution or solid phase peptide synthesis methods are not useful when the amino acids or peptide fragment to be coupled are scarcely soluble, as is the case with the fatty amino acids. Thus, we have experimented with emulsion and detergent-assisted polymerisation techniques, which hitherto have not been effectively explored in peptide synthesis.

In this invention, we have found that by coupling the necessary C-protected (1D-1F) and N- protected (1G-1I) fatty amino acids with carbodiimides in the presence of alcohols capable of forming active esters and a phase transfer catalyst, the homo-oligomers are obtained in high yield even when none of the starting compounds are soluble in the reaction mixture. We illustrate the methods in the Experimental part.

3. Oligomer coupling

The method described in point 2 is not only useful for the stepwise synthesis of oligomers but also for the coupling of already synthesised oligomeric peptides.

By reacting the appropriately protected oligomers, using the methods described above, the expected oligomeric peptides and polymers are obtained in high yield and high purity.

In this way, we have synthesised oligomers containing up to 24 fatty amino acids with the alkyl chains containing 6-24 carbon atoms.

4. Synthesis of hetero-oligomers

To increase the solubility of the fatty amino acid polymers, change their conformation, increase their rate of degradation or biodegradation and confer on them cross linking and pharmaceutical conjugating properties we synthesised oligomers containing:

A) Controlled amounts of the 20 coded and several non coded amino acids, such as lysine, glycine, arginine, phenylalanine, etc.

B) Controlled amounts of derivatised fatty amino acids, including omega-substituents such as: halogen, hydroxyl, carboxyl, amino, cyclopropoxy and amino acids ($-CH(NH_2)COOH$).

Starting from the corresponding dibromo or hydroxybromo alkane we have synthesised amino acids with general formula 1.

where R_1 = halogen-, hydroxyl-, carboxyl-, amino-, cyclo-propoxy-, $-CH(NH_2)COOH-$, guanidino-, thio-alkyl, or alkenyl radical, X=H, N=1, Z=-, P=1, M=-, Y=H.

Following appropriate functional group protection, the standard coded amino acids, or the derivatised fatty amino acids can be incorporated in different positions of the fatty amino acid oligomer chain.

5. Bioactive peptides incorporating fatty amino acids and their derivatives

The incorporation of fatty amino acids into bioactive peptides and their analogues, increases the hydrophobicity of the peptides, protects them from biodegradation and increases their membrane solubility and membrane translocation. Fatty amino acids and their oligomers can be conjugated at the N or C termini and/or incorporated into the polypeptide chain itself.

Our coupling method was used to synthesise compounds with general formula 1.

where R_1, R_2 are alkyl groups with 6-24 carbon atoms, X,Y, and Z are natural amino acids and/or peptides, such as derivatives of enkephalin, LHRH, cimetidine.

6. Conjugates of fatty amino acids and their homo- and hetero-oligomers with pharmaceutical agents

Conjugates with pharmaceutical agents can be used to:

produce prodrugs,

provide a novel formulation method,

increase membrane solubility and/or translocation,

enhance the activity of drugs that act at the membranes,

decrease drug metabolism and increase drug stability,

provide slow and/or controlled release of polymer conjugates.

adjuvants and carriers for vaccines.

Our coupling method was used to synthesise compounds with general formula I

where R_1, R_2 are alkyl groups with 6-24 carbon atoms and X, Y, and Z are pharmaceutical agents such as alkaloids, minoxidil, cephalosporins and others.

7. Higher molecular weight homo- and hetero-polymers of fatty amino acids, their derivatives and other coded amino acids

In addition to the controlled oligomerisation methods mentioned above and described herein, fatty amino acids and their derivatives can be polymerised by first forming the Leuchs anhydrides (Leuchs, H. Ber. Dtsch. Ch m. Ges. 39, 857 (1906); Leuchs, H. and Geiger, W. ibid 41 1721 (1908) or the active esters (Bodanszky, M: Principles of Peptide Synthesis, Springer-

Verlag, Berlin, Heidelberg, New York, Tokyo 1984).

BIOLOGY

Fatty amino acids can be polymerised to form synthetic peptides and proteins that combine the properties of proteins and lipids; in that sense their polymers can be regarded as lipopeptides or lipoproteins or covalent aggregates of lipids. They can be degraded by the endogenous enzymes of microorganisms, plants and mammals to their constituent fatty amino acids which in turn are degraded by transaminases, amino acid oxidases and -oxidation enzymes to natural C2 and/or C3 compounds. Thus, they are biocompatible and biodegradable.

The rates of biodegradation can be increased by increasing the incorporation of L-amino acids or decreased by incorporation of D-amino acids, e.g. D-fatty amino acids.

The hydrophobicity/hydrophilicity index of the synthetic biopeptides is intrinsically high but can be varied by conjugation with hydrophilic amino acids or molecules.

This ability to create polymers and conjugates of differing hydrophobicity and stability that combine that properties of lipids and proteins has important physical and biological consequences. Additionally, by changing the sequence of amino acids, agregates such as micelles or liposomes of differing backbone folding and hence conformations can be constructed.

Although covalent liposomes are not new, those composed of or incorporating fatty amino acids as described herein are novel.

The unique structures and properties of these novel lipopolypeptides and their aggregates can be used advantageously physically, chemically and biologically. The properties include high hydrophobicity, insolubility in

hydrophilic solvents and solubility in hydrophobic solvents/systems, high surface activity, covalent or non-covalent adhesion to surfaces, solubility and compatibility with natural membranes, biocompatibility, biodegradability and non-toxicity.

Specific uses:

1. Formulation:

Fatty amino acids and their oligomers can not only act as counterions to drugs, but as emulsifiers, fillers and solubilisers.

2. Surface active agents:

Free fatty acids form non-covalent aggregates and therefore serve as biocompatible surfactants, detergents, emulsifiers, etc. They can be covalently bound or adsorbed to surfaces and can serve as biocompatible coatings.

Covalent aggregates of fatty amino acids such as monolayers, micelles, and liposomes can be biodegradable or non-biodegradable for reasons described above. Their uses as surfactants, detergents, etc. is readily envisaged.

Other uses of these unique aggregates and conjugates includes (1) biocompatible coatings (e.g. contact lenses, dialysis and transfusion equipment, laboratory glassware, rainproof coatings for wood, metal, concrete and other construction materials), (2) drug conjugates, (3) vaccine conjugation, adjuvants and delivery systems, (4) slow and controlled release of pharmaceuticals, (5) improved oral, I.P., I.V., and transdermal delivery systems, (6) prodrugs, (7) increased shelf life of pharmaceutical preparations involving liposomes, emulsifiers, etc, (8) insulating and protective coatings, (9) polymers to act as synthetic surgical implants.

3. Intrinsic pharmaceutical agents

Because of the structural resemblance of the monomers to membrane lipids and the structural resemblance between covalent fatty acid monolayers and membrane leaflets, fatty acids, their oligomers and conjugates of both readily dissolve in cell membranes. They can therefore affect the intrinsic biological activity of membrane enzymes and proteins. These include cAMP kinases, protein kinase C, tyrosine kinases, lipases, receptors and ion channels; all are proteins involved in transmembrane signalling induced by hormones, growth factors, neurotransmitters, immune modulators, etc.

4. Cosmetics

The surface active and lipid like properties of fatty amino acids, their derivatives and oligomers are of potential value in cosmetic products. Thus the compounds may be used for example in shampoos, conditioners, gels and creams for hair, lotions and soaps for skin care, lipsticks, rouge, foundations and other make-up and beauty products and dental cosmetics.

EXPERIMENTAL

EXAMPLE 1

2-AMINOEICOSANOSIC ACID (1C)

To a 500ml round bottom flask, equipped with reflux condenser, Na (2.5g) was added to ethanol (85ml).

To this solution diethylacetamidomalonate (24.3g,0.11m) and 1-bromo-octane (50g,0.15m) were added and the reaction mixture refluxed for 24 hours. The cold mixture was poured into ice-water (160ml) and the resulting precipitate filtered and washed with water.

The crude solid was placed into a 500ml round bottom flask,

concentrated hydrochloric acid (180ml) and DMF (20ml) added and the mixture refluxed for 24 hours. The cold mixture was poured into a solution of ethanol:water (3:1) and neutralised with conc. ammonium hydrochloride. The precipitate filtered and washed with ethanol:water.

Yield: 34.9g (97%) mp. 237-240°C.

IR(KBr): 3200, 2960, 2920, 2860, 2650, 2340, 2100, 1660, 1625, 1590, 1510, 1420, 1350 cm^{-1}.

Anal. $C_{20}H_{41}NO_2$ (327.6)

Calc. C 73.34 H 12.62 N 4.28 O 9.77

Found C 73.59 H 12.85 N 4.04 O 9.52

EXAMPLE 2

METHYL ω-AMINOEICOSANOATE HYDROCHLORIDE (1F)

In a 500ml round bottom flask equipped with magnetic stirrer, dropping funnel and reflux condenser, thionyl chloride (17.5ml,0.25m) was slowly added to methanol (150ml) at 0°C. Amino acid 1C (8g,0.24m) was added, and the reaction mixture refluxed for 24 hours. 90% of the solvent was removed in vacuo and the precipitated product was filtered and recrystallised from methanol.

Yield: 8.0g (87%) mp. 102-104°C.

IR(KBR): 3200, 2930, 2850, 2620, 2200, 1745, 1595, 1510, 1460, 1450, 1250 cm^{-1}.

NMR($CDCl_3$) 0.9 (3H,t,CH_3), 1.3(32H,m,15xCH_2), 1.35(2H,s,CH_2), 3.5(3H,s,OCH_3), 3.9(1H,m,CH), 9.2(3H, br,s,NH_3)

Anal. $C_{21}H_{44}NO_2Cl$ (378)

Calc. C 66.72 H 11.73 N. 3.70

Found C 66.84 H 11.84 N 3.81

EXAMPLE 3

N-TERT.BUTOXYCARBONYL-α-AMINOEICOSANOIC ACID (1I)

Amino acid 1C (15g,46mmol) was suspended in 2:3 mixture of tert.butanol-water (180ml) and 8M sodium hydroxide was added dropwise to raise the pH to 13. At room temperature ditert.dibutyl-dicarbonate (15g,69mmol) was added in tert.butanol (30ml). The pH was adjusted to 11-12 and the reaction mixture stirred for 2 hours.

The mixture was diluted with water (50ml) solid citric acid added to decrease the pH to 3 and the oil extracted with ethylacetate. After drying ($MgSO_4$) the organic layer was evaporated and the residue triturated with acetonitrile and filtered.

Yield: 8.2g (93%) mp. 79-80°C.

IR(KBR): 3300(NH), 2980, 2920, 2850(CH), 2500(OH), 1700(CO), 1680(CO) cm^{-1}.

NMR($CDCl_3$): 0.9(3H,t,CH_3), 1.24(32H,m,16xCH_2, 1.4(9H,s,$(CH_3)_3C$), 2.2(2H,m,CH_2), 4.2(1H,m, CH), 5.1(1H,d,NH), 10.2(1H,bs,OH)

Anal. $C_{25}H_{49}NO_4$(427.65).

Calc. C 70.21 H 11.55 N 3.27

Found C 70.19 H 11.59 N 3.09

EXAMPLE 4

α-AMINODECANOIC ACID (1A)

The compound was synthesised using the method described in Example 1.

Yield: 87% mp. 259-262°C.

IR(KBR): 3250, 2650, 2150, 2000 (NH_3), 2930, 2910, 2825(CH), 1660, 1625, 1585, 1515, 1410, 1350, 1340, 1090, 930, 885, 720, 700 cm^{-1}.

Anal. $C_{10}H_{21}NO_2$(187.28)

Calc. C 64.13 H 11.30 N 7.48

Found C 64.00 H 11.54 N 7.38

EXAMPLE 5

α-AMINOTETRADECANOIC ACID (1B)

The compound was synthesised according to the procedure outlined in Example 1.

Yield: 89% mp. 218-220°C.

IR(KBR): 3250, 2930, 2910, 2825, 2650, 2150, 2000, 1660, 1625, 1585, 1515, 1410, 1350, 1090, 930, 885, 720, 700 cm^{-1}.

Anal. $C_{14}H_{29}NO_2$(243.39)

Calc. C 69.09 H 12.01 N 5.75

Found C 68.92 H 11.98 N 5.59

EXAMPLE 6

METHYL α-AMINOTETRADECANOATE HYDROCHLORIDE (1E).

The compound was synthesised using the method described in Example 2.

Yield: 92% mp. 103-104°C.

IR(KBR): 2960, 2920, 2850, 2620, 1745($COOCH_3$), 1595, 1515, 1460, 1450, 1410, 1255 cm^{-1}.

EXAMPLE 7

METHYL α-AMINODECANOATE HYDROCHLORIDE (1D).

The compound was synthesised using the method described in Example 2.

Yield 91% mp. 95-97°C.

IR(KBR): 2960, 2920, 2850, 2620, 2200, 1745, ($COOCH_3$), 1595, 1515, 1460, 1450, 1410, 1250 cm^{-1}.

NMR($CDCl_3$): The spectrum identical to 1F, except the m at 1.2 ppm (14H),

3.8ppm (3H,s,$COOCH_3$) and 8.8ppm (3H,s,NH_3^+).

Anal. $C_{11}H_{24}NO_2Cl$ (237.77)

Calc. C 55.57 H 10.17 N 5.89

Found C 55.83 H 10.48 N 5.75

EXAMPLE 8

N-TERT.BUTOXYCARBONYL-α-AMINO-TETRADECANOIC ACID (1H)

The compound was synthesised using the method described in Example 3.

Yield: 89% mp. 58-64°C.

NMR($CDCl_3$): 4.95(1H,s,OCONH), 4.27(1H,m, CH), 1.67(2H,m, CH), 1.42(9H,s,$C(CH_3)_3$), 1.21(20H,m,CH_2), 0.9(3H,s,CH_3).

EXAMPLE 9

N-TERT.BUTOXYCARBONYL-α-AMINO-DECANOIC ACID (1G)

The compound was synthesised using the method described in Example 3.

Yield: 93% mp. 64-66°C.

NMR($CDCl_3$): 4.95(1H,s,OCONH), 4.29(1H,m, CH), 1.85-1.67(2H,m, CH), 1.45(9H,s,$C(CH_3)_3$), 1.27(12H,m,CH_2), 0.88(3H,s,CH_3).

EXAMPLE 10

METHYL N-(N^2-TERT.BUTYOXYCARBONYL-α-AMINO-DECANOYL)-α-AMINOTETRADECANOATE (1O)

Compounds 1H (4.95g, 14.43mmol), and 1E, (4.24, 14.43mmol), triethylamine (2.92g, 28.86mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (3.04g, 15.87mmol), 1-hydroxybenzotriazole hydrate (1.95g, 14.43mmol) and tributyleicosanoyl ammonium sulphate (100mg) in dichloromethane (60ml) at 0°C were stirred for 20 hours.

The reaction was washed with water (2x50ml) and the organic layer dried ($NaSO_4$) and evaporated to dryness. The residue was triturated with methanol, filtered and purified by flash chromatography (CH_2Cl_2:MeOH 10:05).
Yield: 7.40g, (88.2%), mp.66-72.5°C.
NMR($CDCL_3$): 6.49(1H,s,CONH), 4.93(1H,s,OCONH), 4.58, 4.04(2H,s,2xCH), 3.73(3H,s,OCH_3), 1.77(4H,m,2xCH_2), 1.44(9H,s,C(CH_3)$_3$), 1.27(40H,m,20xCH_2), 0.88(6H,t,2xCH_3).

EXAMPLE 11

METHYL N-α-AMINOTETRADECANOYL-α-AMINOTETRADECANOATE HYDROCHLORIDE (1RR)

Compound (10) (1.5g, 2.5mmol) was dissolved in methanol (30ml). A solution of hydrochloric acid in methanol approx. 10M (1.5ml) was added and the solution heated under reflux for 25 minutes. The reaction mixture was cooled, and the solvent removed in vacuum. The residue was crystallised from methanol.
Yield: 1.17g, (90%), mp.69-77°C.
NMR($CDCl_3$): 8.61-8.13(1H,m,CONH), 4.56-4.09(2H,m,2xCH), 3.80-3.69(3H,m,OCH_3), 1.99(4H,m,2xCH_2), 1.23(40H,s,20xCH_2, 0.88(6H,t,2xCH_3).

EXAMPLE 12

N-(N^2TERT.BUTOXYCARBONYL-α-AMINOTETRADECANOYL)-α-AMINOTETRADECANOIC ACID (1PP)

Compound (10) (4.27g,7.34mmol) dissolved in dichloromethane (50ml) and reacted with 1M sodium hydroxide in methanol/water (4:1, 50ml) at room temperature. The progress of the reaction was followed by TLC (CH_2Cl_2:MeOH, 10:1). Upon completion, the organic solvents were removed in vacuo and the mixture acidified with saturated citric acid solution to pH 6. The oil was

extracted with dichloromethane (2x50ml), dried ($NaSO_4$) and the solvent evaporated.

Yield: 3.5g, (85%) of bubbly, vitreous solid mp.69-78°C.

NMR($CDCl_3$): 7.05(1H,m,CONH), 5.40(1H,m,OCONH), 4.55(2H,m,2xCH), 1.87-1.58(4H,m,2xCH_2), 1.43(9H,s,C(CH_3)$_3$), 1.23(40H,s,20xCH_2), 0.88(6H,t,2xCH_3).

EXAMPLE 13

METHYL N-[N^2-(N^3TERT.BUTOXYCARBONYL-α-AMINOTETRADECANOYL)-α-AMINO-TETRADECANOYL]-α- AMINOTETRADECANOATE (1P)

Compounds 1RR (1.92g, 3.7mmol) and 1H (1.27g, 3.7mmol) were reacted using the procedure given in Example 10.

Yield: (2.7g), (81%).

NMR($CDCl_3$): 6.72, 6.56(2H,m,2xCONH), 4.94(1H,s,OCONH), 4.51, 4.39, 4.02(3H,m, 3xCH), 3.71(3H,m,OCH_3), 1.75(6H,m,3xCH_2), 1.44(9H,s,C(CH_3)$_3$9, 1.25(60H,m,30xCH_2), 0.87(9H,t,3xCH_3).

EXAMPLE 14

METHYL N-[N^2-[N^3-(N^4-TERT.BUTOXYCARBONYL-α-AMINOTETRADECANOYL)-α-AMINO-TETRADECANOYL]-α-AMINOTETRADECANOATE-α-AMINOTETRADECANOATE (1R)

Compounds 1PP (3.53g, 6.18mmol) and 1RR (3.20, 6.18mmol) were reacted using the procedure given in Example 10.

Yield: 5.82g, (81%), mp. 150-182°C.

NMR($CDCl_3$): 6.76-6.57(3H,m,3xCONH), 4.91(1H,m,OCONH), 4.5-3.96(4H,m,4xCH), 3.72(3H,s,OCH_3), 1.8-1.63(8H,m,4xCH_2), 1.43(9H,m,C(CH_3)$_3$), 1.25(80H,s,40xCH_2), 0.85(12H,m,4xCH_3).

EXAMPLE 15

METHYL N-[N^1-(-(N^2-α-AMINOTETRADECANOYL-α-AMINOTETRADECANOYL)-α-

AMINOTETRADECANOYL-α-AMINOTETRADECANOATE HYDROCHLORIDE (100)

Compound 1R (1.69g, 1.66mmol) was treated with 1M hydrochloric acid in methanol (20ml) as described in Example 11.

Yield: 1.48g, (93%) of white solid. mp. 152-178°C.

NMR($CDCl_3$): 8.6-7.1(3H,m,3xCONH), 4.43, 4.33(4H,m,4xCH), 3.72(3H,m,OCH_3), 1.79(8H,m,4xCH_2), 1.28(80H,s,40xCH_2), 0.86(12H,m,4xCH_3).

EXAMPLE 16

N-[N^1-[N^2-(N^3-TERT.BUTOXYCARBONYL-α-AMINOTETRADECANOYL)-α-AMINOTETRADECANOYL]-α-AMINOTETRADECANOYL]-α-AMINOTETRADECANOIC ACID. (1NN)

Compound 1R (1.69g, 1.66mmol) was reacted with 1M sodium hydroxide in methanol/water mixture (4:1,10ml) as described in Example 12.

Yield: 1.67g, (78%) of a pale yellow waxy solid. mp. 127-146°C.

NMR($CDCl_3$): 7.44-6.78(3H,m,3xCONH), 5.05(1H,m,OCONH), 4.66-4.02(4H,m,4xCH), 2.0-1.5(8H,m,4xCH_2), 1.43(9H,s,$C(CH_3)_3$), 1.23(80H,s,40xCH_2), 0.85(12H,t,4xCH_3).

EXAMPLE 17

METHYL N-[N^8-TERT.BUTOXYCARBONYL-HEPTA-(α-AMINO-TETRADECANOYL)]-α-AMINO-TETRADECANOATE (1S)

Compounds 100 (951mg, 0.982mmol) and 1NN (1.0g, 0.982mmol) were reacted using the procedure given in Example 10.

Yield: 1.68g (88%) mp. 261-278°C.

NMR($CDCl_3$): 6.9-6.5(7H,m,7xCONH), 4.91(1H,m,OCONH), 4.5-3.9(8H,m,8xCH), 3.72(3H,m,OCH_3), 1.8-1.6(16H,m,8xCH_2), 1.43(9H,m,$C(CH_3)_3$), 1.25(160H,m,80xCH_2), 0.86(24H,m,8xCH_3).

EXAMPLE 18

METHYL N-(N^2-TERT.BUTOXYCARBONYL-α-AMINOEICOSANOYL)-α-AMINOEICOSANOATE (1CC)

Compounds 1F (4.0g, 10.6mmol) and 1L (4.5g, 10.6mmol) were reacted using the procedure given in Example 10.

Yield: 7.2g, (90.5%), mp.68-80°C.

NMR($CDCl_3$): 6.56-6.49(1H,m,CONH), 4.97(1H,m,OCONH), 4.57, 4.05(2H,m,2xCH), 3.72(3H,s,OCH_3O), 1.81-1.63(4H,m,2xCH_2), 1.43(9H,s,$C(CH_3)_3$), 1.25(64H,s,32xCH_2), 0.88(6H,t,2xCH_3).

IR(KBR): 3300, 3040, 2930, 2860, 1750, 1730, 1720, 1680, 1650, 1630 cm^{-1}.

MS(m/e) (%): 752(M+1)(31), 720(28), 703(30), 652(36), 603(15), 518(30), 267(50), 238(41), 216(100), 205(35), 116(55).

EXAMPLE 19

METHYL N-α-AMINOEICOSANOYL-α-AMINOEICOSANOATE HYDROCHLORIDE (1NN)

Compound 1CC (734mg, 0.98mmol) was reacted with hydrochloric acid as described in Example 11.

Yield: 660mg, (100%) of white solid.

NMR($CDCl_3$): 7.61(1H,m,CONH), 4.57, 3.38(2H,m,2xCH), 3.74(3H,s,OCH_3), 1.84, 1.76(4H,m,2xCH_2), 1.27(64H,s,32xCH_2), 0.88(6H,t,2xCH_3).

IR(KBR): 3400, 2980, 2940, 2860, 1735, 1700, 1660 cm^{-1}.

MS(m/e) (%): 652($M+1^+$,22), 337(100), 315(15), 223(40), 188(10), 151(25), 119(20).

EXAMPLE 20

N-(N^2-TERT.BUTOXYCARBONYL-α-AMINOEICOSANOYL)-α-AMINOEICOSANOIC HYDROCHLORIDE (1LL)

Compound 1CC (801mg, 1.06mmol) was treated with hydrochloric acid as described in Example 11.

Yield: 590mg, (75%) of white solid.

NMR($CDCl_3$): 7.05(1H,m,CONH), 5.50, 5.40(1H,m,OCONH), 4.55(2H,m,2xCH), 1.9-1.5(4H,m,2xCH), 1.43(9H,s,$C(CH_3)_3$), 1.23(64H,s,32xCH_2), 0.88(6H,t,2xCH_3).

EXAMPLE 21

METHYL N-[N^2-(N^3-TERT.BUTOXYCARBONYL-α-AMINOEICOSANOYL)-α-AMINOEICOSANOYL]-α-AMINOEICOSANOATE (1DD)

Compound 1MM (1.5g, 2.28mmol) and 1I (976g, 2.88mmol) were reacted using the procedure given in Example 10.

Yield: 2.16g, (92%), mp. 68-72°C.

NMR($CDCl_3$: 6.76, 6.68, 6.59(2H,m,2xCONH), 4.92(1H,m,OCONH), 4.51, 4.39, 4.02(3H,m,3xCH), 3.72(3H,s,OCH_3), 1.70(6H,m,3xCH_2), 1.43(9H,t,$C(CH_3)_3$), 1.26(96H,s,48xCH_2), 0.86(9H,t,3xCH_3).

IR(KBR): 3450, 3040, 2940, 2860, 1745, 1660cm^{-1}.

EXAMPLE 22

METHYL-N-[N^2-[N^2-(N^3-TERT.BUTOXYCARBONYL-α-AMINOEICOSANOYL)-α-AMINOEICOSANOYL]-α-AMINOEICOSANOYL -α-AMINOEICOSANOATE (1EE)

Compounds 1MM (4.66mg, 0.67393mmol) and 1LL (500mg, 0.6793mmol) were reacted using the procedure given in Example 10.

Yield: 840mg, (90%), mp. 78-86°C.

NMR($CDCl_3$): 6.95, 6.82, 6.55(3H,m,3xCONH), 4.92(1H,m,OCONH), 4.53, 4.39, 4.01(4H,m,4xCH), 3.72(3H,c,$COOCH_3$), 1.78(8H,m,4xCH_2), 1.45(9H,s,$C(CH_3)_3$), 1.29(128H,m,64xCH_2), 0.89(12H,t,4xCH_3).

EXAMPLE 23

7,8-DIMETHOXY-14-HYDROXY-ALLOBERNAYL-3-TERT.BUTOXYCARBONYLAMINO-DECANOATE (1L)

7,8-dimethoxy-14-hydroxy-alloberbane (100mg,0,33mmol), 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide hydrochloride (63,3mg, 0.33mmol), triethylamine (34mg, 0.33mmol), and compound 1G (94.7mg, 0.33mmol) in dichloromethane (10ml) were stirred for 4 hours at 0°C.

The reaction mixture was washed with water (3x20ml) and the organic layer dried ($MgSO_4$) and evaporated. The residue was purified by TLC (C_6H_6:MeOH 7:1).

Yield: 82mg (43.6%), gel-like solid mp. 32-38°C.

NMR($CDCl_3$ 6.75, 6.60(2H,s,aromatic H), 3.80, 3.87(6H,s,OCH_3), 5.25. (1H,NH), 3.80(1H,m,$C_{14}H$), 3.75(1H,m, CH), 1.40(9H,s,$C(CH_3)_3$), 1.10(14H,m,7xCH_2), 0.90(3H,t,CH_3).

IR(KBR): 2750-2800 (Bohlmann's absorption)1720, 1660 cm^{-1}(CO).

EXAMPLE 24

METHYL 2-[9,10-(METHYLENEDIOXY)-2-OXO-1,2,3,6,7,11b α-HEXAHYDRO-BENZO[a] QUINOLIZIN-(3)-YL-PROPIONIC-AMINO]-DECANOATE (1K)

In a 50ml round bottom flask equipped with a magnetic stirrer 9,10-(methylenedioxi)-2-oxo-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizin-3-yl-propionic acid (100mg,0.15mmol), compound 1D (76mg, 0.315mmol), triethylamine (64mg, 0.63mmol), 1-hydroxy-benzotriazole hydrate(42.5mg, 0.315mmol) and 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide hydrochloride (63mg, 0.33mmol) in dichloromethane (20ml) were stirred at 0°C for 4 hours The reaction was followed by TLC, CH_2Cl_2:MeOH 10:0.5 $R_{f\ acid}$:0.01, $R_{f\ product}$:0.36, $R_{f\ ester}$:0.43]. The solution was washed with water (3x20ml)

dried ($MgSO_4$) and evaporated. The residue was purified by TLC and recrystallised from ether.

Yield: 107mg (67%) mp. 112-113°C.

IR(KBR): 2750-2800 (Bohlmann's absorption) 1745, 1715(CO, $COOCH_3$), 1660cm^{-1} (CONH).

NMR($CDCl_3$): (6.62, 6.58 (2H,s,aromatic H), 6.00(1H,m,NH), 5.85(2H,s,OCH_2O), 4.60(1H,m, CH), 3.85(3H,s,$COOCH_3$), 1.15(14H,m,7xCH_2), 0.9(3H,t,CH_3).

MS(m/e), (%), $C_{28}H_{40}N_2O_6$ 501(78), 298(100), 270(18), 256(20), 242(60), 226(15), 214(12), 189(28), 176(87), 142(29).

EXAMPLE 25

RAUNESCYL (N^2-TERT. BUTOXYCARBONYL-α-AMINO-TETRADECANOYL)-α-AMINO TETRADECANOATE (1N).

Raunescine (100mg, 0.177mmol) and compound 1PP (100.5mg, 0.177mmol) were reacted as described in Example 10.

Yield: 92mg (46.6%) mp. 96-122°C.

NMR(d-DMSO): 6.65, 6.75, 6.95(4H,s,aromaticH), 4.5(1H,m,axC_{17}-H), 3.85, 3.95(12H,s,$COOCH_3$,OCH_3), 6.5, 5.0(2H,m,NH), 4.65, 4.20(2H,m, CH), 1.9(4H,m, CH), 1.5(9H,s,$C(CH_3)_3$), 1.35(40H,m,20xCH_2), 0.55(6H,t,CH_3).

EXAMPLE 26

METHYL N-[N^2-(N^3-CEPHALORINYL-α-AMINO-EICOSANOYL)-α-AMINO-EICOSANOYL] -α-AMINO EICOSANOATE (1M).

Cephalorine (100mg, 0.24mmol) and 1SS (233mg, 0.24mmol) were reacted using the method described in Example 10.

Yield: 210mg (64%) mp. 152-168°C d!

NMR(d-DMSO-D_2O):8.3, 7.9, 7.1, 6.95, 6.70(9H,m,aromatic, sCH, NCH), 3.6(2H,s,$COCH_2$), 4.1(2H,s,SCH_2), 6.65, 6.55(2H,m,NH), 4.95(1H,m,NH), 4.04,

4,4, 4.5(3H,m, CH), 3.7(3H,s,$COOCH_3$), 1.65, 1.80(6H,m, CH), 1.25, 1.30(96H,m,48xCH_2), 0.9(9H,t,CH_3).

EXAMPLE 27

2-AMINO-12-BROMO-DODECANOIC ACID (1AL)

1,10-Dibromodecane (5g) was refluxed with diethyl-acetamidomalonate (3.62g) in a solution of sodium (384g) in ethanol (19ml) overnight. Water was added to the reaction mixture and extracted with ether. The organic layer, after drying ($MgSO_4$) was evaporated and the residue was refluxed with 12N hydrochloric acid (25ml) for 20 hours.

To the cold reaction mixture ethanol (8ml) was added and the pH wa adjusted to 9 with conc. ammonium hydrochloride. The precipitate was filtered, washed with water and dried.

Yield: 67% mp. 225-235°C.

IR(KBR): 3140, 3020, 2920, 2850, 2660, 2350, 2090, 1730, 1650, 1605, 1575, 1510, 1405, 1340cm^{-1}.

Anal. $C_{12}H_{24}NO_2Br$ (294.23)

Calc. C 48.99 H 8.22 N 4.76

Found C 49.31 H 8.07 N 4.62

EXAMPLE 28

2-AMINO-8-BROMOOCTANOIC ACID (1AN)

1,6-Dibromohexane was reacted using the method described in Example 27.

Yield: 65% mp. 215-225°C.

IR(KBR): 3400, 3000, 2920, 2860, 2660, 2340, 2080, 1730, 1650, 1610, 1575, 1505, 1410, 1340cm^{-1}.

Anal. $C_8H_{16}NO_2Br$ (238.12)

Calc. C 40.35 H 6.77 N. 5.88

Found C 40.30 H 6.69N 5.59

EXAMPLE 29

MORPHINYL TERT.BUTOXYCARBONYL-α-AMINOEICOSANOATE (1J)

In a 50ml round bottom flask equipped with magnetic stirrer, morphine (90mg, 0.293mmol), compound 1I (125mg, 0.293mmol), 1-hydroxy-benzotriazol hydrate (39.6mg, 0.293mmol), triethylamine (29.6mg, 0.293mmol), tributyl-eicosanoyl-ammonium-sulphate (5mg) and 1-ethyl-3-(3-dimethyl-amino-propyl)-carbodiimide hydrochloride (112.3mg, 0.586mmol) in dichloromethane (15ml) were stirred at room temperature for 5 hours.

The reaction mixture was washed with water and the organic layer evaporated after drying ($MgSO_4$). The residue was purified by TLC R_f 1J (CH_2CL_2:MeOH 10:1)=0.33.

Yield: 122mg (58%) gel-like solid.

NMR($CDCl_3$): 6.75, 6.65(2H,s,aromaticH), 5.75(1H,d,C_7-H), 5.28(1H,d,C_8-H), 5.07(1H,m,NH), 4.95(1H,m,C_6-H), 4.49(1H,m, CH), 3.45(1H,m,C_9-H), 3.08, 2.4(2H,m,C_{10}-H), 2.5(3H,s,NCH_3), 1.45(9H,s,$(CH_3)_3C$), 1.3(34H,m,17xCH_2), 0.85(3H,t,CH_3).

EXAMPLE 30

2-AMINO-10-HYDROXY-DECANOIC ACID (1AD).

8-Bromo-octan-1-ol (5,mmol) was dissolved in dichloromethane (40ml) and the solution was stirred at 0°C triethylamine (2.48g,mmol) and acetylchloride (1.92g,mmol) were added and the reaction mixture stirred for a further 3 hours at 0°C and overnight at room temperature.

The mixture was washed with water (3x20ml), the organic layer after

drying (Na_2SO_4) was evaporated.

The crude residue was refluxed overnight with diethyl-acetamidomalonate (5.13g, 24mmol) in a solution of sodium (0.508g, 22mmol) in ethanol (13ml). Water (20ml) was added to the reaction mixture which was then extracted with ether (2x30ml). The organic phase was evaporated and the residue was refluxed with 12N hydrochloric acid (17ml) overnight. Ethanol (8ml) and water (4ml) were added to the solution and cooled to 0°C. The pH was adjusted to 9 and the precipitate was filtered and washed with water. Yield: 4.6g (95%). mp.203-209°C.

IR(KBR): 3150, 3000, 2920, 2860, 2660, 2330, 2100, 1730, 1650, 1570, 1550, 1400, 1335cm^{-1}.

EXAMPLE 31

METHYL 2-AMINO-10-HYDROXY-DECANOATE (1AE)

The compound was synthesised from 1AD as described in Example 2. Yield: 86% mp.°C.

NMR($CDCl_3$): 1.25-1.53(12H,m,6xCH_2), 1.76(2H,p,CH_2), 3.53(3H/t, CH+CH_2-OH), 3.72(3H,s,$COOCH_3$).

EXAMPLE 32

TERT.BUTOXYCARBONYL-2-AMINO-10-HYDROXY-DECANOIC ACID (1AF)

The compound was synthesised from 1AD using the method described in Example 3. The product was purified by TLC.

Yield: 70%

NMR($CDCl_3$): 1.28(10H,s,5xCH_2), 1.45(9H,s,$C(CH_3)_3$), 1.51(1Hm, CH), 1.57(1H,m. CH), 1.75(2H,p,CH_2-CH_2-OH), 3.52(2H,t,CH_2OH), 4.29(1H,t, CH), 5.02(1H,d,NH), 7.0(1H,m,COOH or OH).

EXAMPLE 33

METHYL N-[N^2-(N^3TERT.BUTOXYCARBONYL-α-AMINO-DECANOYL)-α-AMINO-DECANOYL]-2-AMINO-10-HYDROXY-DECANOATE (1AG)

Compounds 1AE (0.49g, 2.24mmol) and 1AH (1.0g,2.24mmol) were reacted using the method described in Example 10.

Yield: 97%.

NMR($CDCl_3$): 0.88(6H,t,2xCH_3), 1.26(34H,m,17xCH_2), 1.45(9H,s,C(CH_3)$_3$), 1.5-2.0(8H,m,4xCH_2), 3.52(2H,t,CH-OH), 3.74(3H,s,OCH_3), 4.02(1H,m, CH), 4.39(m, CH), 4.91(1H,b,NH), 6.52(2H,m,NH).

EXAMPLE 34

METHYL N[N^2-α-AMINODECANOYL-α-AMINODECANOYL]-2-AMINO-10-HYDROXY-DECANOATE HYDROCHLORIDE (1AI)

Compound 1AG (0.7g) was reacted using the method described in Example 2.

Yield: 87% mp.°C.

NMR($CDCl_3$): 0.87(6H,t,CH_3), 1.25, 1.31, 1.42(36H,m,18xCH_2), 1.64, 1.98(4H,m,2xCH_2), 1.75(2H,q,CH-CH_2-OH), 3.52(2H,t,CH_2OH), 3.72(3H,s,OCH_3), 4.37, 4.46(3H,m,3x CH), 8.12, 8.21, 8.41, 8.50, 8.64(5H,m,NH+NH_3^-).

EXAMPLE 35

N-[N^2-(N^3-TERT.BUTOXYCARBONYL-α-AMINO-DECANOYL)-α-AMINO-DECANOYL]-2-AMINO-10-HYDROXY-DECANOIC ACID (1AJ).

Compound 1AG (0.7g) was reacted using the method described in Example 3.

Yield: 97%

NMR($CDCl_3$): 0.87(6H,t,2xCH_3), 1.25, 1.30(36H,m,18xCH_2), 1.43(9H,s,C(CH_3)$_3$), 1.59(2H,p,2x CH_3), 1.75(2H,p,CH_2OH), 1.87(2H,bm,2x CH_2), 3.51(2H,t,CH_2OH, 4.05(1H,m, CH), 4.46(1H,m, CH), 4.56(1H,m, CH), 5.05(1H,bm,NH), 6.95(bm,NH).

EXAMPLE 36

METHYL N-[N^2-[N^3-[N^4-[^{5}-(N^6-TERT.BUTOXYCARBONYL-α-AMINODECANOYL)-α-AMINODECANOYL]-2-AMINO-10-HYDROXYDECANOYL]- -AMINODECANOYL]-α-AMINODECANOYL] -2-AMINO-10-HYDROXYDECANOATE (1AK).

Compounds 1AI and 1AJ were reacted using the method described in Example 10.

Yield: 93%.

NMR($CDCl_3$): 0.87(12H,st,4xCH_3), 1.25(72H,m,36xCH_2), 1.44(s,$ClCH_3$)$_3$), 1.75(12H,bm,6xCH_2), 3.52(4H,t,2xCH_2OH), 3.73(3H,s,OCH_3), 4.0-4.5(b,5x CH), 5.0(1H,b,bocNH), 6.5-7.0(5H,bm,NH).

EXAMPLE 37

METHYL 2-AMINO-12-BROMO-DODECANOATE (1AM)

Compound 1-AL (1g) was stirred with methanol (30ml) and 33% hydrochloric acid in methanol (10ml) at room temperature for 20 hours. The solvents were evaporated at room temperature and the residue titrated with water (5ml) and neutralised with ammonium hydroxide. The precipitated compound was filtered and purified by TLC.

Yield: 75% mp. 186-194°C. (d!).

NMR($CDCl_3$): 1.26(10H,s,5xCH_2), 1.38(3H,m,3xCH), 1.62(1H,m, CH) 1.75(2H,p,CH_2CH_2Br), 3.52(3H,t,CH_2Br+ CH), 3.72(3H,s,$COOCH_3$).

Anal. $C_{13}H_{26}O_2NBr$ (308.26)

Calc. C 50.65 H 8.50 N 4.51

Found C 50.39 H 8.61 N 4.39

EXAMPLE 38

METHYL 2-AMINO-8-BROMOOCTANOATE (1AO)

Compound 1AN was stirred with 1N hydrochloric acid in methanol at room temperature for 20 hours, the solvent was evaporated, the residue dissolved in water and the pH was adjusted to 9 with conc. ammonium hydroxide The mixture was extracted with dichloromethane; the organic phase after drying ($MgSO_4$) was evaporated and the residue then purified by TLC.

Yield: 80% mp. 135-140°C.

IR(KBR): 2930, 2860, 2660, 2560, 2340, 1730, 1670, 1650, 1575, 1450, 1410, 1340cm^{-1}.

Anal. $C_9H_{18}NO_{10}Br$ (252.25)

Calc. C 42.87 H 7.19 N 5.55

Found C 42.65 H 7.41 C 5.37

EXAMPLE 39

1,12-DIAMINO-1,12-DODECANEDICARBOXYLIC ACID (1AP).

1,10-Dibromodecane (5g) was refluxed with diethylacetamido-malonate in a solution of sodium metal (768mg) in ethanol (20ml) for 20 hours. Water (30ml) was added to the reaction mixture and extracted with ether. The ether was evaporated and the oil-like residue was refluxed with 12N hydrochloric acid (40ml) for 20 hours. Ethanol (16ml) and water (8ml) were added to the reaction mixture and the pH were adjusted to 9 with conc. ammonium hydroxide. The precipitated reaction mixture was filtered and washed with water.

Yield: 90% mp. 268-274°C(d!).

IR(KBR): 3400, 3130, 3020, 2905, 2840, 2660, 2350, 2090, 1650, 1620, 1575, 1500, 1400, 1340cm^{-1}.

Anal. $(C_{14}H_{28}N_2)_4$ (288.39).

Calc. C 58.31 H 9.79 N 9.71

Found C 58.28 H 9.81 N 9.51

EXAMPLE 40

RESOLUTION OF DL-METHYL-α-AMINOEICOSANATE (D-1F, L-1F)

To a 100ml three-necked flask, equipped with a magnetic stirrer, gas inlet tube and a Dean-Stark apparatus with a double surface condenser were added the racemic DL-1F (2.0g, 5.29mmol) and toluene (40ml). To this suspension N-methyl-morpholine (0.54ml, 5.29mmol) was added, followed by (-) - (1S,2S,5S)-2-hydroxypinan-3-one (0.8kg, 5.29mmol) and trifluoride diethyletherate and the entire mixture was refluxed for 6 hours under nitrogen. The reaction progress was followed by TLC (hexane-ethylacetate 30-70) and the diastereomeric imines detected at R_f 0.39 and 0.68 respectively. The reaction was over when the ketol (R_f0.48) was no longer detectable. The solvent was removed in vacuo at 30°C, the residue taken up in 40ml of ethylacetate, filtered, washed briefly with brine and water and dried. The resulting yellow oil was used directly for the chromatographic separation of the diasteroisomers on silica gel.

The diasterioisomers were obtained as colourless oils, 0.86g (R_f 0.39) and 0.83g (R_f 0.68) with a yield of 69% overall.

IR(νmax)(thin layer, NaCl): 3440 (OH_{st}), 2980, 2925, 2850, 1745 ($C=O_{st}$, ester), 1650 ($C=N_{st}$), 1460, 1430, 1200, 730, 720 cm^{-1}.

NMR($CDCl_3$): 0.9(3H,t,CH_3; 3H,s,CH_3), 1.2(32H,m,$(CH_2)_{16}$), 1.3(3H,s,CH_3), 1.5(3H,s,CH_3), 1.6-2.7(9H,m,pinane skeleton), 3.7(3H,s,OCH_3), 4.2(1H,m,CH).

MS (Fab): $C_{31}H_{57}NO_3$, MW=491, 492(100), $(M+H)^+$, 474(51), 432(12), 424(29).

Hydrolysis of the diastereoisomeric Schiff Bases

a) Hydrolysis of the Schiff base at R_f 0.69.

To the Schiff base (0.75g, 1.52mmol) dissolved in ethanol (2ml) was added a 0.5m solution of hydroxyamine hydrochloride 4.7ml (1.5x1.52mmol) (EtOH:H_2O, 70:30). The mixture was stirred at room temperature and the white

solid residue taken up in $CHCl_3$ (25ml), washed with 0.1M aq. HCl (2x10ml), 0.5 $NaHCO_3$ (2x10ml), brine and water and dried. The solvent was removed in vacuo and the residue (0.42g) purified on a silica column.

L-Methyl-α-aminoeicosanoate was a colourless oil which upon standing at room temperature solidified to a white powder, 0.32g (58%), mp. 50-51°C.

IR(ν_{max}), (thin layer, NaCl): 3400, 3320,(NH_{st}), 2960, 2920, 2850, 1720($C=O_{st}$, ester), 1620, 1470, 1200, 1170 cm^{-1}.

R_f 0.1.

NMR($CDCl_3$): 0.8(3H,t,CH_3), 1.26(32H,m,$(CH_2)_{16}$), 1.5(2H,m,$-CH_2$), 3.7(3H,s,OCH_3), 4.1(1H,m,CH).

Anal. $C_{21}H_{43}NO_2$, (341.56).

Calc. C 73.85 H 12.68 N 4.10

Found C 73.86 H 12.58 N 4.00

Circular Dichroism spectrum:

The ester exhibited a positive CD spectrum (Fig. 4)

$\Delta\varepsilon$ = + 1.68 (λ_{210}), (c 0.991mg/ml)

By comparison of the CD spectra of this ester and esters of α-aminodecanoic acid (synthesised from enzymatically resolved amino acid) it was possible to assign the L-configuration of the methyl ester obtained from the diastereoisomeric imine with R_f 0.69.

b) Hydrolysis of the Schiff base at R_f 0.38.

The diastereoisomeric imine at R_f 0.38 was hydrolysed as described above to yield the D-isomer as a colourless oil which solidified to a white powder.

mp. 49.5-51.1°C.

Anal. $C_{21}H_{43}NO_2$, (341.56)

Calc. C 73.85 H 12.68 N 4.10

Found C 73.75 H 12.68 N 3.97

Circular Dichroism spectrum:

The ester exhibited a negative spectrum (Fig. 5):

$\Delta\varepsilon$ = - 1.64 (λ_{210}), (c 1.16mg/ml)

This ester was assigned the D-configuration as described above.

EXAMPLE 41

RESOLUTION OF DL-METHYL-α-AMINODECANOATE (D-1O, L-1D)

The method of resolving this ester was similar to the described for the 1F, the quantities of reactants used are as follows:

1.0g(4.21mmol) of 1D HCl

0.43g (4.21mmol) of N-methylmorpholine

40ml anhydrous toluene

100mg boron trifluoride (catalytic)

0.7g (4.19mmol) of (-) -(1S,2S,5S)-2-hydroxypinan-2-one, reaction time was 8 hours.

The diastereoisomeric imines were obtained as colourless oils, R_f 0.32, (0.72g); R_f 0.54, (0.65g), (93%9).

IR(ν_{max}) (thin layer, NaCl): 3440 (OH_{st}), 2980, 2930, 2850, 1745($C{=}O_{st}$), 1650($C{=}N_{st}$), 1460, 1430, 1200, 730, 720cm^{-1}.

NMR($CDCl_3$): 0.9(3H,t,CH_3), 1.2(12H,m,$(CH_2)_6$), 1.3(3H,s,CH_3), 1.5(3H,s,CH_3), 1.6-2.7(9H,m,pinane skeleton), 3.7(3H,s,OCH_3), 4.1(1H,m,CH).

Hydrolysis of the diastereoisomeric imines:

a) Diastereoisomer at R_f 0.54:

To the imine (0.75g, 2.14mmol) in ethanol (2ml) 0.5M ethanolic hydroxyamine hydrochloride (11ml) was added and the solution was stirred at room temperature for 48 hours. The solvents were removed in vacuo at room

temperature and the resulting colourless oil (0.38g) was dissolved in 10ml EtOAc (10ml) and washed as previously decribed. The organic layer was dried and the ester was separated from the ketoxime by chromatography.

The resulting colourless oil was taken up in ethylacetate (5ml) and dry hydrochloric acid gas passed through the solution for 30 mins, and the solvent was removed in vacuo to give a white solid.

Yield: 0.41g (82%), mp: 132-133.5°C.

IR(ν_{max}): 3150, 2960, 2920, 2850, 2600, 2010, 1745, 1610, 1475, 1465, 1460, 1235, 760cm^{-1}.

NMR($CDCl_3$): 0.8(3H,t,CH_3), 1.26(12H,m,$(CH_2)_6$), 1.5(2H,m,$-CH_2$), 3.7(3H,s,OCH_3), 4.1(1H,m,CH), 8.8(3H,brs, NH_3).

Circular Dichroism spectrum:

The ester exhibited a positive CD spectrum, and thus assigned the L configuration.

$\Delta\varepsilon$ = + 1.60 (λ_{210}), (c 1.0mg/ml).

Anal. $C_{11}H_{24}NO_2Cl$,(237.77)

Calc. C 55.57 H 10.17 N 5.89

Found C 55.49 H 10.22 N 5.95

b) Hydrolysis of the diastereoisomer at R_f 0.32:

The method of hydrolysis was as described above, and the quantities of the reactants were as follows:

0.62g (1.77mmol) of the diastereoisomeric imine,

5.3ml (1.5x1.77mmol) of 0.5M ethanolic hydroxylamine hydrochloride.

The imine was dissolved in ethanol (2ml) and following the addition of the hydroxylamine reagent stirring was continued for 50 hours at room temperature.

The ester was obtained as a colourless oil after chromatographic

separation from the ketoxime, 0.28g (79%); it was converted to the hydrochloride salt as previously described.

mp: 130-132°C.

IR(ν_{max}): 3150, 2960, 2920, 2850, 2600, 2010, 1745, ($C{=}O_{st}$, ester), 1610, 1475, 1465, 1460, 1235, 760 cm^{-1}.

NMR($CDCl_3$): 0.8(3H,t,CH_3), 1.26(12H,m,$(CH_2)_{16}$), 1.5(2H,m,CH_2), 3.8(3H,s,OCH_3), 4.1(1H,m,CH), 8.9(3H,brs, NH_3).

Circular Dichroism spectrum:

The ester exhibited a negative CD spectrum,

$\Delta\varepsilon$ = 1.68 (λ_{210}), (c 1.12mg/ml)

and was therefore assigned the D-configuration.

Anal. $C_{11}H_{24}NO_2Cl$, (237.77)

Calc. C 55.57 H 10.17 N 5.89

Found C 55.33 H 10.13 N 5.87

EXAMPLE 42

RESOLUTION OF DL-METHYL-α-AMINOTETRADECANOATE (D-1E, L-1E)

The method for resolving this methyl ester is as described in Example 40 and the quantities of reactants used are as follows:

2.0g (6.81mmol) of the racemic hydrochloride

0.68g (6.81mmol) of redistilled N-methylmorpholine

50ml of anhydrous toluene

1.14g (6.78mmol) of (-)-(1S,2S,5S)-2-hydroxypinan-2-one, and 100mg of boron trifluoride diethetate as catalyst. Reaction time was 8 hours.

The two diastereoisomeric imines were obtained as slightly yellowish clear oils; 1.13 g (R_f0.58), 1.4g (R_f0.38), the overall yield was 2.53g (92%).

IR(ν_{max}), (thin layer, NaCl): 3440(OH_{st}), 2980, 2930, 2855 (CH_{st}), 1745 ($C{=}O_{st}$), 1655 ($C{=}N_{st}$), 1460, 1430, 1195 cm^{-1}.

NMR($CDCl_3$): 0.9(3H,t,CH_3; 3H,s,CH_3), 1.2(20H,m,$(CH_2)_{10}$), 1.3(3H,s,CH_3), 1.5(3H,s,CH_3), 1.6-2.8(9H,m,), 3.8(3H,s,OCH_3), 4.4(1H,m,CH).

Hydrolysis of the diastereoisomeric Schiff bases

The method is as previously described in Example 40.

a) Hydrolysis of the Schiff base at R_f 0.58.

Yield: 0.43g (94%), mp. 113°C.

IR (ν_{max}): 3200, 2960, 2859, 2600, 2000, 1745($C=O_{st}$), 1600, 1590, 1475, 1465, 1460, 1235.

NMR($CDCl_3$): 0.9(3H,t,CH_3), 1.25(20H,m,$(CH_2)_{10}$), 1.38(2H,m,$-CH_2$), 3.5(3H,s,OCH_3), 4.0(1H,m,CH), 9.1(3H, brs, NH_3).

R_f 0.52

Circular Dichroism spectrum:

The ester exhibited a positive CD spectrum,

$\Delta\varepsilon$ = + 2.1 (λ_{210}), (c 1.29mg/ml)

By comparison with enzymatically resolved 1D this enantiomer was assigned the L configuration.

Anal. $C_{15}H_{32}NO_2Cl$, (293.88)

Calc. C 61.31 H 10.98 N 4.77

Found C 61.07 H 11.20 N 4.60

b) Hydrolysis of the Schiff base at R_f 0.38.

To the diastereoisomeric imine (0.8g, 1.97mmol) 0.5M ethanolic hydroxylamine hydrochloride [6.6ml, (1.5x2.21mmol)] was added and the solution stirred at room temperature for 96 hours.

A further hydroxylamine reagent (6.6ml) were added and stirring was continued for a further 48hours. The product was isolated in pure form as described above and converted to the hydrochloride salt to yield 0.42g (91%) of a white powder.

mp: 112.114°C.

R_f 0.51.

Both the IR and the proton NMR spectra of this enantiomer were identical to the L-enantiomer.

Circular dichroism spectrum:

The CD spectrum was negative

$\Delta\varepsilon = -2.43$ (λ_{210}), (c 0.995mg/ml)

This enantiomer has been assigned the D configuration.

Anal. $C_{15}H_{32}NO_2Cl$, (293.88)

Calc. C 61.31 H 10.98 N 4.77

Found C 60.92 H 10.63 N 4.63

EXAMPLE 43

METHYL N-(N^2TERT.BUTOXYCARBONYL-α-AMINODECANOYL)-α-AMINODECANOATE (1Z)

Compounds 1G and 1D were reacted using the method described in Example 10.

Yield 92%, mp. 33-38°C.

NMR($CDCl_3$): 6.60, 6.52(1H,m,CONH), 5.00(1H,m,OCONH), 4.57, 4.08(2H,m,2xCH), 3.73(3H,s,OCH_3), 1.80, 1.65, 1.58, 1.43(9H,s,$C(CH_3)_3$9, 1.23(24H,s,12xCH_2), 0.85(6H,t,2xCH_3).

EXAMPLE 44

METHYL N-[N^2-(N^3-TERT.BUTOXYCARBONYL-α-AMINODECANOYL)-α-AMINODECANOYL]-α-AMINODECANOATE (1X)

Compounds 1AH and 1D were reacted using the method described in Example 10.

Yield: 91%, mp. 97-101°C.

NMR($CDCl_3$): 6.68, 6.56(2H,m,2xCONH), 4.96(1H,m,OCONH), 4.51, 4.39, 4.02(3H,m,

3xCH), 3.71(3H,s,OCH_3), 1.75(6H,m,3xCH_2), 1.43(9H,s,$C(CH_3)_3$), 1.25(36H,s,18xCH_2), 0.85(9H,t,3xCH_3).

EXAMPLE 45

METHYL-N-[N^2-[N^3-(N^4-TERT.BUTOXYCARBONYL-α-AMINODECANOYL)-α-AMINODECANOYL]-α-AMINODECANOYL]-α-AMINODECANOATE (1Y)

Compounds 1GG and 1G were reacted using the method given in Example 10.

Yield 92%, mp. 151-160°C.

NMR($CDCl_3$): 6.96, 6.86, 6.79, 6.59(3H,m,3xCONH), 4.86(1H,m,OCONH), 4.50, 4.40, 4.33, 4.01, 3.94(4H,m,4xCH), 3.72(3H,s,OCH_3), 1.82-1.70(8H,m,4xCH_2), 1.25(48H,s,24xCH_2), 1.43(9H,s,$C(CH_3)_3$), 0.87(12H,t,4xCH_3).

EXAMPLE 46

METHYL N-[N^5-TERT.BUTOXYCARBONYL-TETRA-(α-AMINODECANOYL)]-α-AMINODECANOATE (1V)

Compounds 1AS and 1G were reacted using the method described in Example 10.

Yield: 93% 192-200°C (d!).

NMR($CDCl_3$: 6.95-6.58(4H,m,4xCONH), 4.96(1H,m,OCONH), 4.51-3.94(5H,m,5xCH), 3.72(3H,m,OCH_3), 1.82-1.68(10H,m,5xCH_2), 1.44(9H,s,$C(CH_3)_3$), 1.24(60H,m,30xCH_2), 0.87(15H,t,5xCH_3).

EXAMPLE 47

METHYL N-[N^6-TERT.BUTOXYCARBONYL-PENTA(α-AMINODECANOYL]-α-AMINODECANOATE (1W)

Compound 1FF and 1GG were reacted using the method described in Example 10.

Yield: 91%

NMR($CDCl_3$): 6.96-6.53(5H,m,5xCONH), 4.85(1H,m,OCONH), 4.51-3.94(6H,m,6xCH), 3.73(3H,s,OCH_3), 1.82-1.66(12H,m,6xCH_2), 1.44(9H,s,$C(CH_3)_3$), 1.24(72H,m,36xCH_2). 0.88(18H,m,6xCH_3).

EXAMPLE 48

METHYL N-[N^{12}-TERT.BUTOXYCARBONYL-UNDECA(α-AMINODECANOYL)]-α-AMINODECANOATE (1AA)

Compounds 1HH and 1II were reacted using the method decribed in Example 10.

Yield 90%

NMR($CDCl_3$): 6.96-6.51(11H,m,11xCONH), 4.86(1H,m,OCONH), 4.52-3.93(12H,m,12xCH), 3.72(3H,m,OCH_3), 1.82-1.67(24H,m,12xCH_2), 1.44(9H,s,$C(CH_3)_3$), 1.24(144H,m,72xCH_2), 0.88(36H,m,12xCH_3).

EXAMPLE 49

METHYL N-[N^{24}-TERT.BUTOXYCARBONYL-TRIEICOSA-(α-AMINODECANOYL] -α-AMINODECANOATE (1BB)

Compounds 1FF and 1KK were reacted using the method described in Example 10.

Yield 90%.

NMR($CDCl_3$): 6.97-6.54(23H,m,23xCONH), 4.86(1H,m,OCONH), 4.52-3.93(24H,m,24xCH), 3.72(3H,m,OCH_3), 1.83-1.68(48H,m,24xCH_2), 1.43(9H,s,$C(CH_3)_3$), 1.24(288H,m,14xCH_2), 0.87(72H,m,24xCH_3).

EXAMPLE 50

N-(N^2-TERT.BUTOXYCARBONYL-α-AMINODECANOYL)-α-AMINODECANOIC ACID (1AH)

Compound 1Z was treated with sodium hydroxide using the method

described in Example 12.

Yield 100%, mp. 77-85°C.

NMR($CDCl_3$), 8.5(1H,s,COOH), 7.05(1H,m,CONH), 5.50, 5.40(1H,m,OCONH), 4.55(2H,m,2xCH), 1.87, 1.70, 1.58(4H,m,2xCH_2), 1.43(9H,s,$(CH_3)_3$), 1.23(24H,s,12xCH_2), 0.85(6H,t,2xCH_3).

EXAMPLE 51

N-[N^2-(N^3-TERT.BUTOXYCARBONYL-α-AMINODECANOYL)-α-AMINODECANOYL] - α-AMINODECANOIC ACID (1FF).

Compound 1X was treated with sodium hydroxide using the method described in Example 11.

Yield 93%.

NMR($CDCl_3$): 8.5(1H,s,COOH), 7.69-7.05(2H,m,2xCONH), 5.50(1H,m,OCONH), 4.55, 4.32, 4.21(3H,m,3xCH), 1.86-1.55(6H,m,3xCH_2), 1.44(9H,s,$C(CH_3)_3$), 1.23(36H,s,18xCH_2), 0.86(9H,t,3xCH_3).

EXAMPLE 52

N[N^6-TERT.BUTOXYCARBONYL-PENTA-(α-AMINODECANOYL)]-α-AMINODECANOIC ACID (1HH)

Compound 1W was treated with sodium hydroxide using the method described in Example 12.

Yield 95%.

NMR($CDCl_3$): 7.70-7.05(5H,m,5xCONH), 5.50(1H,m,OCONH), 4.56-4.20(6H,m,6xCH), 1.87-1.55(12H,m,12xCH_2), 1.44(9H,s,$C(CH_3)_3$), 1.23(72H,s,36xCH_2), 0.86(18H,t,6xCH_3).

EXAMPLE 53

N-[N-TERT.BUTOXYCARBONYL-UNDECA-(α-AMINODECANOYL)]-α-AMINODECANOIC ACID (1FF)

Compound 1AA was treated with sodium hydroxide using the method given in Example 12.

Yield 91%.

NMR($CDCl_3$): 7.70-7.03(11H,m,11xCONH), 5.50(1H,m,OCONH), 4.57-4.19(12H,m,12xCH), 1.88-1.55(24H,m,12xCH_2), 1.44(9H,s,$C(CH_3)_3$), 1.23(144H,m,72xCH_2), 0.86(36H,m,12xCH_3).

EXAMPLE 54

METHYL N-AMINODECANOYL-α-AMINODECANOATE HYDROCHLORIDE (1AZ)

Compound 1Z was refluxed with hydrochloric acid in methanol according to the method described in Example 11.

Yield 100%.

NMR($CDCl_3$): 8.21, 8.13, 8.07(1H,m,1xCONH), 4.45, 4.37, 4.32(2H,m,2xCH), 3.80, 3.74, 3.69(3H,m,OCH_3), 2.03, 1.80(4H,m,2xCH_2), 1.23(24H,s,12xCH_2), 0.85(6H,t,2xCH_3).

EXAMPLE 55

METHYL N-(N^2-α-AMINODECANOYL-α-AMINODECANOYL)-α-AMINODECANOATE HYDROCHLORIDE (1GG)

Compound 1X was refluxed with hydrocloric in methanol according to the method described in Example 11.

Yield 100%

NMR($CDCl_3$): 8.22-8.06(2H,m,(2xCONH), 4.45-4.30(3H,m,3xCH), 3.80-3.69(3H,m,OCH_3), 2.03-2.79(6H,m,3xCH_2), 1.24(36H,m,18xCH_2), 0.85(9H,m,3xCH_3).

EXAMPLE 56

METHYL N-PENTA-(α-AMINODECANOYL)-α-AMINODECANOATE HYDROCHLORIDE (1II)

Compound 1W was refluxed with hydrochloric acid in methanol according to the method described in Example 11.

Yield 100%

NMR($CDCl_3$): 8.23-2.04(5H,m,5xCONH), 4.48-4.30(6H,m,6x CH), 3.81-369(3H,m,OCH_3), 2.05-1.79(12H,m,6xCH_2), 1.24(72H,m,36xCH_2), 0.85(18H,m,6xCH_3).

EXAMPLE 57

METHYL N-UNDECA(α-AMINODECANOYL)-α-AMINODECANOATE HYDROCHLORIDE (1KK).

Compound 1AA was reacted with hydrochloric acid in methanol according to the method described in Example 11.

Yield 100%

NMR($CDCl_3$): 8.24-8.03(11H,m,11xCONH), 4.48-4.28(12H,m,12xCH), 3.81-3.69(3H,m,OCH_3), 2.05-1.78(24H,m,12xCH_2), 1.24(144H,m,72xCH_2), 0.85(36H,m,12xCH_3).

EXAMPLE 58

L-1Z

L-1D and L-1G were reacted as described in Example 43.

Yield: 85% mp. 32-33°C.

α_D^{20}=-22° (in hexafluoroisopropanol) C=1

Anal. $C_{26}H_{50}N_2O_5$(470.75)

Calc. C 66.34 H 10.70 N 5.95

Found C 66.58 H 10.86 N 6.70

EXAMPLE 59

L-1X

L-1D and L-1AH was reacted as described in Example 44.

Yield: 86% mp. 113-114°C.

α_D^{20}=-31.2° (in hexafluoroisopropanol) C=1.

Anal. $C_{36}H_{69}N_3O_6$ (639.96)

Calc. C 67.57 H 10.87 N 6.57

Found C 67.83 H 10.99 N 6.73

EXAMPLE 60

L-1Y

L-1D and L-1FF was reacted using the method described in Example 45.

Yield: 81% mp. 212-213°C.

α_D^{20}=-36.6° (in hexafluoroisopropanol) C=1

Anal: $C_{46}H_{88}N_4O_7$(809.22)

Calc. C 68.30 H 10.96 N 6.92

Found C 67.91 H 10.71 N 7.01

EXAMPLE 61

L-1V

L-1G and L-1AS were reacted using the method described in Example 46.

Yield: 79% mp. 231-233°C.

α_D^{20}=-41° (in hexafluoroisopropanol) C=1

Anal. $C_{56}H_{107}N_5O_8$(978.49)

Calc. C 68.71 H 11.02 N 7.16

Found C 69.12 N 11.11 N 7.28

EXAMPLE 62

L-1W

L-1G and L-1AT were reacted using the method described in Example 47.

Yield: 80% mp. 255-257°C.

α_D^{20}=-43.9° (in hexafluoroisopropanol) C=1

Anal. $C_{66}H_{126}N_6O_9$(1147.75)

Calc. C 69.07 H 11.06 N 7.30

Found C 68.98 H 11.10 N 7.35

EXAMPLE 63

[L-α-AMINOTETRADECANOYL]^{10}-LHRH (1ZZ)

N-tert.butoxycarbonyl-α-amino-tetradecanoic acid (0.171g,0.55mmol) was incorporated onto chloromethyl resin (0.7g; 0.7 meq/g substitution) as the cesium salt. The tert-butoxycarbonyl group was removed by treatment of the amino acid-resin conjugate with 40% trifluoroacetic acid in dichloromethane and the polypeptide built in a stepwise fashion according to normal solid phase peptide synthesis methodologies. Deprotection of the LHRH derivative with anhydrous hydrofluoric acid and purification by reverse phase, semi-preparative HPLC afforded 200mg of pure peptide (33% of theoretical yield based upon the deprotected material). Purified LHRH derivative was characterised by FAB-MS.

M^+, 1351

EXAMPLE 64

[D-α-AMINODECANOYL]^6, [L-2-AMINOTETRADECANOYL]^{10}-LHRH (1XX) AND [D-α-AMINODECANOYL]^1, [L-α-AMINOTETRADECANOYL]^{10}-LHRH (1YY)

N-tert.butoxycarbonyl-α-amino-tetradecanoic acid-resin conjugate (0.86, 0.5mmol amino acid) and the peptides were assembled as described above.

After HF treatment and semipreparative reverse phase HPLC 0.15g of 1XX (22%) and 0.12g (17%) of 1YY were obtained.

M^+ (1XX) 1383

M^+ (1YY) 1409

EXAMPLE 65

L-2-AMINOTETRADECANOYL)^5-ENKEPHALINE (1VV) AND

(D-ALA)^3,(L-α-AMINOTETRADECANOYL)^5-ENKEPHALINE (1WW)

L-N-tert.butoxycarbonyl-α-amino-tetradecanoic acid-resin conjugate (0.5mmol final susbstitution) was prepared as described for compound 1ZZ). The two peptides were assembled using solid phase peptide synthesis methods and released from the solid support by treatment with HF; this afforded 0.160g (48%) and (1VV) and 0.180g (54) of (1WW).

M^+ (VV) 668

M^+ (WW) 682

EXAMPLE 66

(L-α-AMINODECANOYL-L-α-AMINODECANOYL-GLYCYL)$_N$ (AVERAGE N=15), (1AB) AND (L-α-AMINODECANOYL-L-PHENYLANANYL-GLYCYL)$_N$ (AVERAGE N=20) (1AC).

The tripeptide, methyl L-N-tert.butoxycarbonyl-α-amino-decanoyl-L-α-aminodecanoyl-glycylate was assembled in 80% yield using routine solution peptide synthesis methods. The methyl protecting group was removed by treating the peptide (1g, 1.9mmol) for 20 mins with 3 equivalents of alcoholic potash. pH neutralisation with citric acid and extraction with ethyl acetate gave 0.8g (81%) of peptide free acid. This was converted into the p-nitrophenyl ester using p-nitrophenol (0.22g, 1.6mmol) and dicycloexylcarbodiimide (0.33g, 1.6mmol) in dichloromethane (15ml). After 12

hours of reaction the urea was removed by filtration and the organic solution washed with water, alkaline solution and acid solution. 0.7g (71%) of peptide p-nitrophenyl ester was thus obtained. The fully protected peptide was then treated with dry hydrochloric acid in dichloromethane for 25 mins to remove the tert. butoxycarbonyl group. The solvent and excess hydrochloric acid were then removed and the peptide used for the polymerisation step without further purification. The polymerisation was carried out in dimethylsulphoxide (20ml) in the presence of catalytic amounts of triethylamine and at 50 degrees for 12 hours. At the end of the reaction the solvent was removed in vacuo, the oily material resuspended in toluene and the organic layer washed with alkaline solution to remove p-nitrophenyl alcohol. Removal of the solvent gave 0.2g of a flaky solid. Compound (1AC)) was prepared in an identical fashion and 0.3g (30% of polymeric material was obtained.

The average molecular weight was determined by laser light-scattering. The average number of repeating tripeptide unit, n, was found to be 15 for (1AB) and 20 for (1AC).

EXAMPLE 67

METHYL N^1-[N^2-(N^3-TERT.BUTYLOXYCARBONYL-L-ALANYL)-α-AMINODECANOYL]-α-AMINO DECANOATE (1AX)

Compound 1AZ hydrochloride (1 eq), tert-butyloxy carbonyl-L-alanine (1 eq), 1-hydroxybenzotriazole (1 eq), tetrabutylammonium chloride (5 mg), triethylamine (2 eq) and 1-ethyl-3(3-dimethylamino propyl) carbodiimide hydrochloride (1 e) were reacted together in dichloromethane at 0°C in an ice-bath. The reaction was allowed to come to room temperature overnight as the ice-bath melted. The reaction mixture was then washed with water twice and the organic layer collected, dried (Na_2SO_4) and evaporated. The

residue was purified by TLC.

Yield: 92%

NMR($CDCl_3$): 0.88(6H,t,2xCH_3), 1.25(27H,s,12xCH_2 and CH_3), 1.45(9H,s,C(CH_3)$_3$), 1.65(2H,m, -CH_2), 1.84(2H,m, -CH_2), 3.73(3H,m,OCH_3), 4.00 & 4.37(1H,multiplets, -CH), 4.39 & 4.54(2H, multiplets, 2 -CH), 4.95 & 5.06(1H,m, & d, ^{t}BOC-NH), 7.35(1H,m,NH), 7.67 & 7.81(1H,broad peaks,NH).

Anal. $C_{29}H_{55}N_3O_6$ (541.77)

Calc. C 64.29 H 10.23 N 7.76

Found C 64.00 H 10.52 N 7.52

EXAMPLE 6S

METHYL α-(N-TERT.BUTOXYCARBONYL)-AMINODECANOYL-α-AMINODECANOYL-L-ALANYL-α-AMINODECANOYL-α-AMINODECANOATE (1AR)

Methyl L-alanyl-α-aminodecanoyl-α-aminodecanoate-hydrochloride (1AY) (1 eq), α-(N-t-compound 1AH(1 eq), 1-hydroxybenzotriazole (1 eq), triethylamine (2 eq) tetrabutylammonium sulphate (5 mg) and 1-ethyl-3(3-dimethylaminopropyl) carbodiimide hydrochloride (1 eq) were stirred in dichloromethane at 0°C in an ice-bath. The reaction was allowed to come to room temperature overnight as the ice-bath melted. The reaction mixture was then washed with water twice. The organic layer was collected, dried (Na_2So_4) and evaporated. The residue was purified by TLC.

Yield: 96%

NMR($CHCl_3$): 0.88(12H,t,4xCH_3), 1.25(51H,s,24xCH_2+CH_3), 1.45(9H,s,C(CH_3)$_3$), 1.64(4H,m,2xCH_2), 1.83(4H,m,2xCH_2), 3.72(3H,m,OCH_3), 4.0-4.5(5H,broad peaks,5x -CH), 5.0(1H,broad, ^{t}BOC-NH-), 7.3-7.8(4H, broad peaks, 4 peptide NH).

Anal. $C_{49}H_{93}N_5O_8$ (880.3024)

Calc. C 66.86 H 10.65 N 7.96

Found C 66.59 H 10.62 N 7.67

EXAMPLE 69

POLY-L-α-AMINODECANOIC ACID (L-1AV)

Compound L-1A (10mmol) was suspended in dioxane (100ml) and the suspension saturated with phosgene. The reaction was stirred at room temperature for 12 hours and the solvent removed in vacuo. The oily residue was redissolved in chloroform and the Leuch anhydride precipitated by the addition of hexane. The decyl-4-oxazolidine-2,5-dione was dried and used for polymerisation without further purification.

To a 10% solution of decyl-4-oxazolidine-2,5-dione, a catalytic amount of potassium carbonate was added and the solution stirred at room temperature for 5 days. The resultant polymer was collected by filtration.

Yield: 64%

The number of amino acid units was determined by gel exclusion and laser scattering.

EXAMPLE 70

POLY-L-α-AMINOTETRADECANOIC ACID (L-1A)

Compound L-1B (10mmol) was converted to the Leuch anhydride and polymerised using the method described in Example 69.

Yield: 41%

EXAMPLE 71

POLY-L-α-AMINOEICOSANOIC ACID (L-1A)

Compound L-1C (10mmol) was converted to the Leuch anhydride and polymerised using the method described in Example 69.

Yield: 46%

EXAMPLE 72

CO-POLYMER OF L-α-AMINO-DECANOIC ACID AND LYSIN (1BA)

Compound L-1A (10mmol) and lysin (10mmol) were reacted using the method described in Example 69.

Yield: 52%

EXAMPLE 73

CO-POLYMER OF L-α-AMINO-DECANOIC ACID AND PHENYLALANINE (1BB)

Compound L-1A (10mmol) and phenylalanine (19mmol) were reacted using the method described in Example 69.

Yield: 60%

EXAMPLE 74

CO-POLYMER OF L-α-AMINO-DECANOIC ACID AND GLUTAMINE (1BC)

Compound L-1A (10mmol) and glutamine (10mmol) were reacted using the method described in Example 69.

Yield: 48%

EXAMPLE 75

CO-POLYMER OF L-α-AMINO-TETRADECANOIC ACID AND LYSIN (1BD)

Compound L-1B (10mmol) and lysin (10mmol) were reacted using the method described in Example 69

Yield: 70%

EXAMPLE 76

CO-POLYMER OF L-α-AMINO-TETRADECANOIC ACID AND PHENYLALANINE (1BE)

Compound L-1B (10mmol) and phenylalanine (10mmol) were reacted using

the method described in Example 69.

Yield: 68%

EXAMPLE 77

CO-POLYMER OF L-α-AMINO-TETRADECANOIC ACID AND GLUTAMINE (1BF)

Compound L-1B (10mmol) and glutamine (10mmol) were reacted using the method described in Example 69.

Yield: 60%

EXAMPLE 78

CO-POLYMER OF L-α-AMINO-EICOSANOIC ACID AND LYSIN (1BG)

Compound L-1C (10mmol) and lysin (10mmol) were reacted using the mthod described in Example 69.

Yield: 56%

EXAMPLE 79

CO-POLYMER OF L-α-AMINOEICOSANOIC ACID AND PHENYLANINE (1BH)

Compound L-1C (10mmol) and phenylalanine (10mmol) were reacted using the method described in Example 69

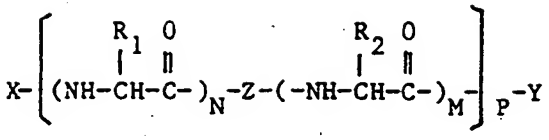
Yield: 55%

EXAMPLE 80

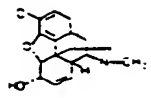
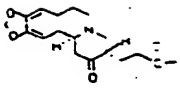
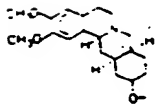
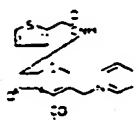
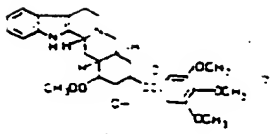
CO-POLYMER OF L-α-AMINO-EICOSANOIC ACID AND GLUTAMINE (1BI)

Compound L-1C (10mmol) and glutamine (10mmol) were reacted using the method described in Example 69.

Yield: 45%



GENERAL FORMULA 1

Compound								
	N	M	P	Z	R_1	R_2	X	Y
A	1	-	1	-	$CH_3-(CH_2)_7$	-	H	OH
B	1	-	1	-	$CH_3-(CH_2)_{11}$	-	"	"
C	1	-	1	-	$CH_3-(CH_2)_{17}$	-	"	"
D	1	-	1	-	$CH_3-(CH_2)_7$	-	"	OCH_3
E	1	-	1	-	$CH_3-(CH_2)_{11}$	-	"	"
F	1	-	1	-	$CH_3-(CH_2)_{17}$	-	"	"
G	1	-	1	-	$CH_3-(CH_2)_7$	-	$(CH_3)_3COCO$	OH
H	1	-	1	-	$CH_3-(CH_2)_{11}$	-	"	"
I	1	-	1	-	$CH_3-(CH_2)_{17}$	-	"	"
J	1	-	1	-	$CH_3-(CH_2)_{17}$	-	"	
K	1	-	1	-	$CH_3(CH_2)_7$	-		OCH_3
L	1	-	1	-	$CH_3(CH_2)_7$	-	$(CH_3)_3COCO$	
M	3	-	1	-	$CH_3(CH_2)_{17}$	-		OCH_3
N	3	-	1	-	$CH_3(CH_2)_{17}$	-	$(CH_3)_3COCO$	

Compound								
1	N	M	P	Z	R_1	R_2	X	Y
O	2	-	1	-	$CH_3(CH_2)_{11}$	-	$(CH_3)_3COCO$	OCH3
P	3	-	1	-	"	-	"	"
R	4	-	1	-	"	-	"	"
S	8	-	1	-	"	-	"	"
Z	2	-	1	-	$CH_3(CH_2)_7$	-	"	"
X	3	-	1	-	"	-	"	"
Y	4	-	1	-	"	-	"	"
V	5	-	1	-	"	-	"	"
W	6	-	1	-	"	-	"	"
AA	12	-	1	-	"	-	"	"
BB	24	-	1	-	"	-	"	"
CC	2	-	1	-	$CH_3(CH_2)_{17}$	-	"	"
DD	3	-	1	-	"	-	"	"
EE	4	-	1	-	"	-	"	"
FF	3	-	1	-	$CH_3(CH_2)_7$	-	"	OH
GG	3	-	1	-	"	-	H	OCH_3
HH	6	-	1	-	"	-	$(CH_3)_3COCO$	OH
II	6	-	1	-	"	-	H	OCH_3
JJ	12	-	1	-	"	-	$(CH_3)_3COCO$	OH
KK	12	-	1	-	"	-	H	OCH_3
LL	2	-	1	-	$CH_3(CH_2)_{17}$	-	$(CH_3)_3COCO$	OH
MM	2	-	1	-	"	-	H	OCH_3
NN	4	-	1	-	$CH_3(CH2)_{11}$	-	$(CH_3)_3COCO$	OH
OO	4	-	1	-	"	-	H	OCH_3
PP	2	-	1	-	"	-	$(CH_3)_3COCO$	OH

Compound	N	M	P	Z	R_1	R_2	X	Y
RR	2	-	1	-	$CH_3(CH_2)_{11}$	-	H	OCH_3
SS	3	-	1	-	$CH_3(CH_2)_{17}$	-	H	OCH_3
ZZ	1	-	1	-	$CH_3(CH_2)_{11}$	-	des[Gly]^{10} LHRH	OH
XX	1	-	1	-	$CH_3(CH_2)_{11}$	-	[D-2-aminodecanoyl]^{6} des [Gly]^{10}-LHRH	OH
YY	1	-	1	-	"	-	[D-2-aminodecanoyl]^{1} des [Gly]^{10}-LHRH	OH
VV	1	-	1	-	"	-	des[Leu]^{5}-enkephaline	OH
WW	1	-	1	-	"	-	[D-Ala]^{3},des [Leu]^{5}enkephaline	OH
AB	1	1	15	$CH_3(CH_2)_7$ HN-CH-CO	$CH_3(CH_2)_7$	H	H	OH
AC	1	1	20	L-Phe	"	H	H	OH
AD	1	-	1	-	"	-	H	OH
AE	1	-	1	-	"	-	H	OCH_3
AF	1	-	1	-	"	-	$(CH_3)_3COCO$	OH
AG	2	1	1	-	$CH_3(CH_2)_7$	$HO(CH_2)_8$	"	OCH_3
AH	2	-	1	-	"	-	"	OH
AI	2	1	1	-	"	$HO(CH_2)_8$	H	OCH_3
AJ	2	1	1	-	"	"	$(CH_3)_3COCO$	OH
AK	2	1	2	-	"	"	"	OCH_3
AL	1	-	1	-	$Br-(CH_2)_{10}$	-	H	OH
AM	1	-	1	-	"	-	H	OCH_3
AN	1	-	1	-	$Br(CH_2)_6$	-	H	OH
AO	1	-	1	-	"	-	H	OCH_3

Compound								
	N	M	P	Z	R_1	R_2	X	Y
AP	1	-	1	-	$(CH_2)_{10}\underset{NH_2}{CH}-COOH$	-	H	OH
AR	2	2	1	Ala	$CH_3(CH_2)_7$	$CH_3(CH_2)_7$	$(CH_3)_3COCO$	OCH_3
AS	4	-	1	-	"	-	-	OCH_3
AT	5	-	1	-	"	-	-	OCH_3
AZ	2	-	1	-	"	-	H	OCH_3
AX	-	2	1	Ala	"	$CH_3(CH_2)_7$-	$(CH_3)_3COCO$	OCH_3
AY	-	2	1	Ala	"	-	H	OCH_3
AV	90-100	-	1	-	$CH_3(CH_2)_7$	-	H	OH
AW	90-100	-	1	-	$CH_3(CH_2)_{11}$	-	H	OH
AU	90-100	-	1	-	$CH_3(CH_2)_{17}$	-	H	OH
BA*	1	-	50	Lys	$CH_3(CH_2)_7$	-	H	OH
BB*	1	-	45	Phe	"	-	H	OH
BC*	1	-	50	Glu	"	-	H	OH
BD*	1	-	40	Lys	$CH_3(CH_2)_{11}$	-	H	OH
BE*	1	-	40	Phe	"	-	H	OH
BF*	1	-	45	Glu	"	-	H	OH
BG*	1	-	35	Lys	$CH_3(CH_2)_{17}$	-	H	OH
BH*	1	-	40	Phe	"	-	H	OH
BI*	1	-	40	Glu	"	-	H	OH

*Due to the random amino acid order of the asterisked copolymers, precise information regarding composition and sequence is not obtainable.

CLAIMS

The embodiment of the invention for which an exclusive property and privilege is claimed are defined as follows:

1. a. Racemic and optically active compounds, their salts and therapeutic compositions of general formula 1 to be used as

(i) Pharmaceutical formulation components, including:

- counter ions,
- covalent and non-covalent aggregates including micelles and liposomes,
- agents for controlled or slow release preparations,
- transdermal delivery agents,
- covalent drug conjugates including prodrugs.

(ii) Surface active agents, including:

- detergents, emulsifiers and foaming and antifoaming agents,
- biocompatible coatings for contact lenses, dialysis and transfusion equipment, laboratory glassware and other uses,
- weatherproof coatings for wood, metal, concrete and other construction materials.

(iii) Intrinsic pharmaceutical agents for:

- actions on cell membranes and membrane proteins, including effects on transmembrane signalling,
- other actions.

(iv) Cosmetics, including:

- dental preparations,
- skin care preparations,
- make-up preparations,
- hair preparations,

- bathing preparations.

where X=H, alkoxycarbonyl, aryloxycarbonyl, peptide, amino acid, pharmaceutical agent, Y=OH, O=alkyl, O-aryl, substituted O-alkyl or O-aryl, peptide, amino acid or pharmaceutical agent, Z=amino acid, peptide, diamino diacid, pharmaceutical agent, substituted fatty amino acid R_1,R_2=linear, branched or substituted (halogen, -OH,-COOH,NH_2,-CH(NH_2)COOH, -cyclopropoxy, -pharmaceutical agent, -amino acid or peptide) alkyl- or alkenyl- group of 1-24 carbon atoms, N, M, P = 0-100.

b. Processes for producing compounds with general formula 1. The synthesis of fatty amino acids was achieved by hydrolysis and partial decarboxylation of 2-acetoamido-2-ethoxycarbonyl-linear, branched or substituted alcanoic acids in hydrochloric acid/water/dimethyl formamide.

The coupling of fatty amino acid monomers and oligomers with other fatty amino acids monomers and oligomers, other amino acids and peptides (including substituted fatty amino acids and their oligomers) and pharmaceutical agents was carried out in polar organic solvents in the presence of a phase transfer catalyst, a carbodiimide and an alcohol capable of forming an active ester.

The polymerisation of fatty amino acid monomers and oligomers and the copolymerisation of fatty amino acid monomers and oligomers with other amino acids was carried out by reacting either the Leuchs anhydrides or active esters of the amino acids in the presence of base.

2. Processes as claimed in Claim 1 wherein for the hydrolysis and decarboxylation 10-20% of dimethyl formamide in hydrochloric acid/water was used.

3. Processes as claimed in Claim 1 wherein for the coupling a polar organic solvent, preferably dimethyl sulphoxide, dimethyl formamide or dichloromethane, was used.

4. Processes as claimed in Claim 1 wherein catalytic amounts of a phase transfer catalyst preferably tert. alkyl-ammonium salts (tributyl-eicosanoyl-ammonium-bromide) were used for the coupling.

5. Processes as claimed in Claim 1 wherein alcohols which form active esters were used for the coupling, preferably 1-hydroxy-benzotriazole.

6. Processes as claimed in Claim 1 wherein carbodiimides preferably 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide were used for the coupling.

7. Compounds and processes as claimed in Claim 1 wherein mono and/or oligo fatty amino acids with linear, branched or substituted alkyl or alkenyl chains up to 24 carbon atoms were used for the coupling.

8. Compounds and processes as claimed in Claim 1 wherein one or both alkyl or alkenyl chains were substituted with halogen, -OH, -COOH,- amino acid, -$NH-_2CH(NH_2)COOH$, -cyclopropoxy,-pharmaceutical agents, -alkaloids, -cephalosporins, -minoxidil or -peptides (LHRH, enkephalin).

9. Compounds and processes as claimed in Claim 1 wherein the monomer and/or homo- and hetero-oligomer chain is coupled with amino acids, peptides and pharmaceutical agents.

10. Compounds and processes as claimed in Claim 1 wherein racemic or optically active fatty amino acids were used for the coupling.

11. Compounds and processes as claimed in Claim 1 wherein fatty amino acids and/or coded or other amino acids were polymerised or copolymerised through Leuchs anhydrides or active esters yielding random and block polymers with different distributions and percentages of the amino acid constituents.

12. Compounds and processes as claimed in Claim 1 wherein compounds of general formula 1 form salts with inorganic or organic acids, salts or ions (hydrochloric acid, citric acid, tartaric acid, sodium ion, etc).

13. Compounds and processes as claimed in Claim 1 wherein the compounds of

general formula 1 are used as counter ions in pharmaceutical formulations, such as anionic or cationic forms of the fatty acid monomers or oligomers.

14. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula 1 are used to form covalent or non-covalent aggregates in pharmaceutical formulation, such as liposomes consisting of polymerised fatty amino acids or micelles consisting of monomeric or oligomeric species.

15. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula 1 are used as agents for controlled or slow release pharmaceutical formulations.

16. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula are used as agents for transdermal drug delivery in pharmaceutical formulations.

17. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula are used to form covalent drug conjugates, including prodrugs, adjuvants and carriers in pharmaceutical and immunological formulation.

18. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula 1 are used for their surface active properties, particularly as detergents, emulsifiers, foaming and anti-foaming agents, and cosmetic agents.

19. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula 1 are used as biocompatible coatings such as for contact lenses, dialysis and transfusion equipment and laboratory glassware, cosmetics, etc.

20. Compounds and processes as claimed in Claim 1 wherein the compounds of general formula 1 are used as coatings for wood, metal, concrete and other construction materials.

21. Compounds and processes as claimed in Claim 1 wherein the compounds of

general formula 1 are used as pharmaceutical and immunological agents in their own right, for their actions on cell membranes and membrane associated proteins, including effects on transmembrane signalling and other effects.

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